Serotonergic Control of Cerebellar Mossy Fiber Activity by Modulation of Signal Transfer by Rat Pontine Nuclei Neurons

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Möck, Martin, Cornelius Schwarz, and Peter Thier. Serotonergic control of cerebellar mossy fiber activity by modulation of signal transfer by rat pontine nuclei neurons. J Neurophysiol 88: 549–564, 2002; 10.1152/jn.00015.2002. Serotonergic modulation of precerebellar nuclei may be crucial for the function of the entire cerebellar system. To study the effects of serotonin (5-HT) on neurons located within the pontine nuclei (PN), the main source of cerebellar mossy fibers, we performed standard intracellular recordings from PN neurons in a slice preparation of the rat pontine brain stem. Application of 5 μM 5-HT significantly altered several intrinsic membrane properties of PN neurons. First, it depolarized the somatic membrane potential by $6.5 \pm 3.5 \text{ mV}$ and increased the apparent input resistance from $49.5 \pm 14.6$ to $62.7 \pm 21.1 \text{ MΩ}$. Second, 5-HT altered the I-V relationship of PN neurons: it decreased the inward rectification in hyperpolarizing direction, but increased it when depolarizing currents were applied. Third, it decreased the rheobase from $0.32 \pm 0.14$ to $0.24 \pm 0.14 \text{ nA}$ without affecting the firing threshold. Finally, the amplitude of medium-duration afterhyperpolarizations was reduced from $-14.9 \pm 2.0$ to $-12.3 \pm 2.4 \text{ mV}$. Together, these 5-HT effects on the intrinsic membrane properties result in an increase in excitability and instantaneous firing rate. In addition, application of 5 μM 5-HT also modulated postsynaptic potentials (PSPs) evoked by electrical stimulations within the cerebral peduncle. The amplitude, maximal slope, and integral of these PSPs were reduced to $46.2 \pm 23.4\%$, $45.7 \pm 23.7\%$, and $61.4 \pm 28.4\%$ of the control value, respectively. In contrast, we found no change in the decay and voltage dependence of PSPs. To test modulatory effects on short-term synaptic facilitation, we applied pairs of electrical stimuli at intervals between 10 and 1,000 ms. 5-HT selectively enhanced the paired-pulse facilitation for interstimulus-intervals >20 ms. The alteration of paired-pulse facilitation points to a presynaptic site of action for 5-HT effects on synaptic transmission. Pharmacological experiments suggested that pre- and postsynaptic effects of 5-HT were mediated by two different kinds of 5-HT receptors: changes in intrinsic membrane properties were blocked by the 5-HT$_2$ receptor antagonist cinanserin while the reduction of PSPs was prevented by the 5-HT$_4$ receptor antagonist cyanoindol. In conclusion, 5-HT increases the excitability of PN neurons but decreases the synaptic transmission on them. The selective enhancement of synaptic facilitation may, however, allow high-frequency inputs to effectively drive PN neurons, thus the PN may act as a high-pass filter during periods of 5-HT release.

INTRODUCTION

The cerebellum receives its input via two different afferent systems, the climbing and the mossy fibers. While the sole source of climbing fibers is the inferior olive, the vast majority of mossy fibers in mammals arise from the pontine nuclei (PN). It is well documented that the membrane properties of inferior olivary neurons are massively influenced by serotonin [5-hydroxytryptamine (5-HT)] in vivo and in vitro (Goldstein et al. 1969; Headley et al. 1976; Placantonakis et al. 2000; Sugihara et al. 1995). In particular, the rhythmic firing and subthreshold oscillations are under control of serotonergic neurons located within medullary raphe and reticular nuclei (Placantonakis et al. 2000). Thus the “working state” of the climbing fiber system is subject to serotonergic modulation. Such detailed information is lacking for the mossy fiber system. Our present knowledge about a possible serotonergic regulation of information transfer and processing within the PN is limited. More than a decade ago, Mihailoff et al. (1989) demonstrated projections from well-established serotonergic regions like the pontine and medullary raphe nuclei to retrograde tracing from the PN. Interestingly, parts of these structures, namely the medullary raphe nuclei, also provide serotonergic input to the inferior olive (Bishop and Ho 1986; Compoin and Buisseret-Delmas 1988). Since then, the presence of 5-HT receptors within the PN has been implicated by in situ hybridization studies and immunocytochemistry (Cornea-Hérbert et al. 1999; Hamada et al. 1998; Pompeiano et al. 1994; Wright et al. 1997). However, the functional consequences of these serotonergic afferents and receptors have as yet not been explored.

5-HT is one of the best-known neuromodulators, affecting many neurons throughout the whole CNS (Jacobs and Azmitia 1992). The diversity of 5-HT receptor types (Hoyer and Martin 1997) is in line with the diversity of actions 5-HT exerts on its target cells (for review, see Anwyl 1990). Most receptor types act on second messenger systems increasing or decreasing membrane conductances as well as synaptic transmission. Using a brain slice preparation (Möck et al. 1997; Schwarz et al. 1997), we have recently shown that the PN possess many of the putative pre- and postsynaptic targets known to be modulated by 5-HT in other preparations. On this basis, it is plausible to speculate that also the second cerebellar input system, arising from the PN, is under serotonergic control. In this study we tested whether 5-HT affects the membrane properties and synaptic transmission in PN neurons in vitro. Our results clearly demonstrate distinct effects on both the excitability and...
the synaptic transmission via two different receptor types allowing the PN to function as frequency filter, which can be adjusted according to functional needs.

**METHODS**

Slice preparation and maintenance, the basic in vitro electrophysiology techniques, data sampling, and analysis methods employed in this study resemble those described elsewhere (Möck et al. 1997; Schwarz et al. 1997). Briefly, Sprague-Dawley rats (18–25 days old) were deeply anesthetized with ketamine and decapitated. During the dissection of the brain, care was taken not to impose mechanical stress onto the brain stem. To cool the brain as fast as possible, the dissection was performed under the superfusion of cold (4°C) artificial cerebrospinal fluid (ACSF; see following text). Parasagittal slices were cut to a thickness of 400 μm using a vibrating microtome (Leica, Wetzlar, Germany). They were stored in ACSF containing (in mM) 123 NaCl, 5 KCl, 1.25 NaH2PO4, 2 MgCl2, 26 NaHCO3, 2 CaCl2, and 10 d-glucose, oxygenated with 95% O2-5% CO2 at room temperature. For recording, the slices were transferred to a submerged recording chamber and superfused with ACSF at 35°C.

Standard intracellular current-clamp recordings were performed with glass microelectrodes filled with 3 M potassium acetate (50–100 MΩ) using an Axoclamp 2A amplifier (Axon Instruments) in the bridge mode. The microelectrodes had a linear I-V relationship within −1.0–1.0 nA. The voltage records were low-pass filtered (cutoff frequency 10 kHz) and digitized at a sampling rate of 5 kHz or 20 kHz using a PC with a 1401plus interface and Spike2 software (Cambridge Electronic Design, Cambridge, UK).

Postsynaptic potentials (PSPs) were evoked by applying negative current pulses of 0.1-ms duration via lacquer-coated tungsten electrodes (impedance, 2.5–7 MΩ, at 1 kHz). The stimulation electrode was placed into the cerebral peduncle. Square current pulses were generated by a constant current bipolar stimulus isolator (A365R; WPI) and controlled by the 1401plus interface. If not explicitly noted otherwise, current pulses were delivered at frequencies of 0.075 or 0.15 Hz during data recording. The minimal stimulus intensity required to elicit PSPs was determined for every individual neuron. To study the intensity dependence of PSPs, the intensity was increased from these thresholds in 5–10-μA steps until spikes were generated, or to 250 μA maximal. PSPs were recorded at a sampling rate of 10 kHz. For every stimulus intensity or every test membrane potential, 10 trials were recorded subsequently. To monitor changes in apparent membrane resistance, small negative current pulses (−0.1 nA; 200-ms duration) were applied via the recording electrode 300 ms before the test stimulus. The interval between the two current pulses was 5 ms. Passive feedback was employed to readjust the somatic membrane potential to the value measured during control recordings. Recovery was recorded in all experiments as long as the recording was stable enough. Every neuron served as its own control.

For statistical comparison of control and test recordings, we employed the Wilcoxon signed-rank test for paired samples (Systat; SPSS). A first-order error probability of P < 0.05 was considered as significant.

**RESULTS**

Intracellular recordings obtained from 79 PN neurons were accepted for analysis according to the criteria described in Schwarz et al. (1997). Briefly, neurons were included in our sample if they developed a stable resting potential within a few minutes after implantation and if the apparent membrane resistance was ≥15 MΩ. Furthermore, only neurons with spike amplitudes of more than 50 mV (measured from the resting potential to the peak) and a spike width no greater than 1 ms (measured at half-amplitude between resting potential and peak of the spike) were accepted. Under control conditions, none of these neurons was spontaneously active. They displayed a resting membrane potential of −67.4 ± 4 (SD) mV. Most likely the neurons used in the present study were impaled at the soma, and therefore the membrane potential measurements may not be directly valid for distal parts of the cells. To take this into account, we will use the term somatic membrane potential (SMP). The apparent membrane resistance (Rm) was 49.5 ± 14.6 MΩ, and the apparent membrane time constant (τ) was 6.6 ± 2.0 ms. Rm and τ were determined from voltage responses to small negative current pulses (−0.1 nA) to minimize contamination by activation of voltage-dependent conductances. As even small negative current pulses activate a fast and sustained inward rectification in PN neurons (Schwarz et al. 1997), the true passive membrane properties may be slightly different.

**5-HT effects on membrane potential responses to subthreshold stimuli**

In all cells tested (n = 79), application of 5 μM 5-HT led to a significant (P < 0.001) and persistent depolarization of the SMP (Fig. 1, A, B, D, and F). In 22% of the neurons, the depolarization was strong enough to drive the SMP above the firing threshold, causing previously silent cells to fire spontaneously (Fig. 1, B and D). In these cases, measuring the steady-state level of 5-HT-induced depolarization was not possible, and therefore we determined the maximal depolarization before firing occurred. On average the neurons were depolarized by 6.5 ± 3.5 mV. Removal of 5-HT resulted in a complete recovery of the initial SMP within a few minutes (Fig. 1, A, B, and D). Population data are given in Fig. 1F.

The 5-HT-induced depolarization of the SMP was accompanied by a significant (P < 0.001) and reversible increase of the Rm from 49.5 ± 14.6 to 62.7 ± 21.1 MΩ (n = 79). No such change was observed for τ. 6.6 ± 2.0 ms under control conditions versus 6.8 ± 2.3 ms under 5-HT (P > 0.2). Population data for Rm are given in Fig. 1G. It is important to take the increase of Rm into account for the analysis of membrane potential responses to current stimuli. Because changes in Rm per se alter membrane potential responses, analysis of 5-HT–induced alterations independent of changes in Rm required a correction of the quantified data according to these changes in Rm, i.e., by a factor derived from the ratio between Rm values measured under both conditions. In the following, data corrected for changes in Rm are indicated by a (∗). Characteristically, the I-V relationship of PN neurons shows a fast inward rectification in response to negative and subthreshold positive current pulses of 200-ms duration (Fig. 2, A and C, left). The strength of inward rectification depends on the extracellular potassium concentration (Schwarz et al. 1997).
Moreover, inward rectification is altered to outward rectification in response to positive current pulses when sodium channels are blocked with tetrodotoxin (Schwarz et al. 1997). Application of 5 μM 5-HT reversibly weakened the inward rectification in response to negative current pulses (Fig. 2, B and C, left). The summary plot in Fig. 2C (right) shows the deviation of the I-V curves after 5-HT application from the ones obtained from control recordings fitted by a linear regression ($r = 0.454$). In contrast to the membrane potential responses to hyperpolarizing current pulses, 5-HT reversibly enhanced inward rectification in depolarizing direction (Fig. 2, B and C). Since only small positive current pulses were subthreshold, and therefore available for analysis, this enhancement is not very conspicuous. Statistical analysis, however, revealed a significant ($P < 0.05$) difference to the control values for current pulses between 0.1 and 0.3 nA.
5-HT effects on membrane potential responses to suprathreshold stimuli

As previously described by Schwarz et al. (1997), depolarizing current pulses driving the SMP of PN neurons just above the firing threshold usually elicit one single action potential that is followed by a pronounced afterhyperpolarization (AHP; Figs. 3A and 5A). In response to higher current amplitudes, PN neurons fire a train of action potentials with a marked firing rate adaptation (Fig. 4, A and B). In the present sample, the firing threshold was $-45.4 \pm 3$ mV and the rheobase (i.e., the minimal current necessary to reach firing threshold) was $0.32 \pm 0.14$ nA. After superfusion with 5 µM 5-HT, we observed...
observed no change in firing threshold ($-45.4 \pm 3 \text{ vs. } -45.6 \pm 3.5 \text{ mV after } 5\text{-HT}$). In contrast, there was a decrease of the rheobase to $0.24 \pm 0.14 \text{ nA (0.28 \pm 0.16 nA$); the mean contribution of changes in $R_m$ to the decrease in rheobase was 53%). This decrease was significant ($P < 0.001$) for both the uncorrected and the corrected values. Population data are shown in Fig. 3, B and C.

The typical firing behavior of PN cells is shown in Fig. 4. Once the depolarizing current application is strong enough to drive the SMP clearly above firing threshold, the cell responded with a train of action potentials, which displayed a substantial firing rate adaptation (Fig. 4A, left). To quantify the adaptation, we plotted the duration of the interspike interval (ISI) versus the spike number in the train for each trial (Fig. 4B). Typically, the slope of the resulting curves was positive at all stimulus amplitudes, indicating firing rate adaptation. However, they differed in steepness for different current amplitudes. The steepest curves were obtained with lower current amplitudes, and firing rate adaptation decreased when the amplitude current was increased. Furthermore, the firing rate of PN neurons typically increased with higher current amplitudes. The current-frequency relationship was fairly linear in the range of current amplitudes tested (Fig. 4C, left). According to the marked firing rate adaptation, the instantaneous firing rate was highest for the first ISI and reached almost constant levels at the end of the stimuli. Application of 5 $\mu M$ 5-HT had clear effects on the firing behavior of PN neurons (Fig. 4A, right).

First, previously subthreshold current amplitudes (0.3 and 0.4 nA in the example shown) now caused the neuron to fire spikes. Second, similar suprathreshold current amplitudes evoked higher numbers of spikes, i.e., a higher firing frequency under 5-HT. The increase in instantaneous firing frequency was typically highest during the first ISIs (Fig. 4C, right). However, 5-HT did not cause a qualitative change of the firing behavior. All neurons tested showed strong adaptation under both conditions. An increase in firing rate without change in adaptation raised the question of whether this increase was based solely on the increase in $R_m$. To test whether other factors also contribute to the firing rate increment by 5-HT, we compared the current amplitude needed to evoke five spikes under control conditions with the corrected current amplitude (i.e., corrected for the increase in $R_m$, eliciting the same number of spikes after 5-HT application. The mean current amplitude was $0.63 \pm 0.15 \text{ nA under control conditions and } 0.58 \pm 0.20 \text{ nA$ (uncorrected, 0.49 \pm 0.17 \text{ nA$ under 5-HT. The Wilcoxon signed-ranks test yielded a significant difference at a probability level of $P < 0.01$ ($n = 64$). Therefore we conclude that the 5-HT-induced increase in firing rate cannot be explained purely by an increase in $R_m$ (in this case the changes in $R_m$ accounted for 42% of the 5-HT effect). This notion is further supported by the current-frequency plot for the entire population in Fig. 4D (top left). As stated above, the current-frequency curves for individual neurons were fairly linear (see example in Fig. 4C); we therefore used polynomial fits of first order for the population plot. These polynomial fits (fitted to the mean of the normalized values for any current amplitude) show the mean instantaneous firing rate for each ISI plotted versus the current amplitude under control conditions and the corrected current amplitude under 5-HT. The amount of change in instantaneous firing rate was estimated by subtraction of the corresponding fit curves. As shown in Fig. 4D (bottom left), the change in normalized firing rate was about...
5% at any current amplitude for the first ISI (whereas it was about 43% if changes in $R_{in}$ were neglected). These differences, as well as those obtained for the second ISI (about 3%, data not shown), were significant ($P < 0.05$). In contrast, as exemplified by the differences for the fifth ISI, the normalized firing rates of the following ISIs were not significantly different between both conditions. Thus in particular for the first two ISIs, the increase in $R_{in}$ is not entirely sufficient to account for the increase in instantaneous firing rate.

PN neurons possess membrane conductances responsible for the generation of at least two kinds of AHPs: one of medium duration (~50 ms; mAHP) immediately following each spike,

![Graph](image-url)
and one (sAHP) lasting several hundreds of milliseconds, which requires the generation of several spikes to be initiated (Schwarz et al. 1997). While the influence on the firing rate exerted by the sAHP is thought to be restricted to later parts of a spike train due to its late onset, the mAHP supposedly controls each ISI. The mAHP is therefore a likely candidate for the remaining 5-HT influence on the firing rate of PN neurons not accounted for by changes in $R_m$. To test this possibility, we measured the amplitudes of mAHPs (defined as the difference between firing threshold and the negative peak of the mAHP) before and after 5-HT application. These measurements were done using depolarizing intracellular stimuli just strong enough to elicit a single spike and thus a single mAHP (Fig. 3A). The superposition of corresponding membrane potential trajectories recorded before (black trace) and after 5-HT application (gray trace) as shown in Fig. 5A clearly indicate a substantial reduction of the mAHP amplitude. The summary plots in Fig. 5, B and C, demonstrate that similar reductions were found in almost every cell tested. The statistical analysis revealed a significant difference at a probability level of $P < 0.001$ (for both uncorrected and corrected values). In the present sample, the mean mAHP amplitude was $-14.9 \pm 2.0$ mV under control conditions and $-12.3 \pm 2.4$ mV ($-10.4 \pm 2.6$ mV) under 5-HT. From these results, it may be concluded that a joint increase in $R_m$ and decrease in mAHP amplitude accounts for the 5-HT-induced enhancement of firing rate observed in PN neurons.

**Pharmacology of 5-HT–induced modulation of the membrane properties**

To fully understand the serotonergic modulation of PN neurons, it is necessary to identify the receptor types involved. In
this study, we used cinanserin and cyanopindolol, two broad antagonists of 5-HT$_2$ and 5-HT$_1$ receptors, respectively, to block 5-HT action on PN neurons. Application of 5 µM 5-HT in the presence of 10 µM cyanopindolol still substantially depolarized the SMP. As shown in Fig. 1C, the depolarization was strong enough to evoke spontaneous firing in several cases. In contrast, coapplication of 10 µM cinanserin largely prevented a depolarization of the SMP (Fig. 1E). Summary data for the entire population are given in Fig. 1F. As noted above, the 5-HT–induced depolarization of the SMP was accompanied by an increase in $R_{in}$ (Fig. 1, A, B, and D). A similar increase occurred during application of 5-HT plus cyanopindolol (Fig. 1, C and G), whereas no such change in $R_{in}$ was detectable during coapplication of 5-HT and cinanserin (Fig. 1, E and G). Mean values and statistical analysis are given in Table 1. Similar results were obtained for the effects of 5-HT receptor antagonists on the $I-V$ relationships of PN neurons. As shown in Fig. 2D (left), cyanopindolol was not able to prevent 5-HT–induced weakening of inward rectification in hyperpolarizing direction and enhancement of inward rectification in depolarizing direction. The plot shows the deviations of the $I-V$ curves obtained from recordings under 5-HT and 5-HT plus cyanopindolol from those under control conditions. No significant ($P < 0.5$) difference between the two test populations ($n = 6$) was observed. In contrast, cinanserin ($n = 6$) largely reduced the 5-HT effects on the $I-V$ curves of PN neurons (Fig. 2D, right). The remaining difference between control condition and 5-HT/cinanserin coapplication was not significant ($P > 0.1$). Next, we tested the effects of cyanopindolol and cinanserin on the serotonergic modulation of the mAHP amplitude (Fig. 5, B and C, Table 1). Cyanopindolol was not able to significantly prevent 5-HT–induced reduction of mAHPs. In contrast, blocking 5-HT$_2$ receptors with cinanserin was sufficient to obtain mAHP amplitudes, which were not significantly different from the control values. Finally, probing the pharmacology of 5-HT action on the rheobase (Fig. 3B and Table 1) revealed a tendency in favor of a 5-HT$_2$ receptor–mediated decrease in rheobase. This possibility was, however, not substantiated by statistical significance. In summary, 5-HT–induced changes in SMP, $R_{in}$, mAHP amplitude, inward rectification, and rheobase were all blocked by cinanserin but not by cyanopindolol. Therefore the serotonergic modulation of these intrinsic membrane properties can be explained by activation of 5-HT$_2$ receptors.

5-HT effects on PSPs

5-HT receptors are located at the soma, along dendrites, along axons, and at the presynaptic terminals in different brain regions (Cornea-Hébert et al. 1999; DeFilipe et al. 2001; Hamada et al. 1998; Sari et al. 1999). Thus 5-HT may also modulate the synaptic transmission on the neurons within these regions. Consequently, we asked whether this is true for PN neurons. In the rat, PN neurons receive massive synaptic input from the entire cerebral cortex (Legg et al. 1989) and numerous subcortical structures (Mihailoff et al. 1989). We have recently described the characteristics of the PSPs in rat PN neurons in vitro (Möck et al. 1997).

In this study we investigated how 5-HT acts on PSPs in PN neurons that were elicited by applying small current pulses (5–250 µA, 0.1 ms) at sites within the cerebral peduncle, which include the cerebropontine fibers. Typically, these stimuli evoked excitatory PSPs with short latencies (0.8–5.0 ms), a fast rise, and a slower decay (Fig. 6, A and B). To quantitatively assess 5-HT effects, we determined several characteristic parameters of the PSPs. The magnitude is well characterized by the peak amplitude, their time course by the maximal slope (for the rising phase), and the time required to decay from the peak to half-maximal amplitude ($t_{1/2}$ PSP). Finally, the time integral was calculated as measure for magnitude and total length of the PSPs.

Our routine paradigm was to determine the minimal stimulus intensity, i.e., the smallest current amplitude that evoked detectable PSPs (>3 times the SD of the noise), for each neuron under control conditions, followed by application of successively larger stimulus amplitudes (until spikes were generated). The same stimulus intensities were then used to test synaptic transmission during 5-HT application. To allow comparison between control and test experiments, the 5-HT–induced depolarization of the SMP was compensated by constant current injection. Figure 6 shows two representative examples of PSP

### Table 1. Quantified effects of 5-HT and 5-HT receptor antagonists on membrane properties

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>5-HT</th>
<th>5-HT/Cyanopindolol</th>
<th>5-HT/Cinanserin</th>
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<td></td>
<td>SMP (mV)</td>
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<tr>
<td>Cinanserin Group</td>
<td>$-67.1 \pm 3.9$</td>
<td>$-58.8 \pm 4.3$</td>
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<td>$R_{in}$ (MΩ)</td>
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<tr>
<td>Cinanserin Group</td>
<td>$65.5 \pm 21.5$</td>
<td>$85.5 \pm 35.1$</td>
<td>$71.0 \pm 27.3$</td>
<td>$8$</td>
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<tr>
<td></td>
<td>mAHP (mV)</td>
<td></td>
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<tr>
<td>Cinanserin Group</td>
<td>$-13.0 \pm 1.8$</td>
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<td>$7$</td>
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<td>Rheobase (nA)</td>
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<td>Cinanserin Group</td>
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Values are ± SE. *values corrected for changes in $R_{in}$; 5-HT, 5-hydroxytryptamine; SMP, somatic membrane potential; $R_{in}$, membrane resistance; mAHP, medium afterhyperpolarization.
in PN neurons and their modulation by 5-HT. Under control conditions, the minimal stimulus intensities evoked PSPs with mean amplitudes of 1.71 ± 1.66 mV, mean maximal slope of 1.25 ± 1.16 mV/ms, mean \( t_{1/2} \) of 6.15 ± 3.69 ms, and mean integral of 6.12 ± 3.57 V·s. Elevation of stimulus intensities resulted in a nonuniform increase of all PSP parameters (Fig. 6, C and D). We have proposed that this reflects a successive recruitment of additional fibers or fiber bundles (Möck et al. 1997). Application of 5 \( \mu \)M 5-HT substantially reduced the magnitude of the PSPs at any given stimulus intensity (Fig. 6).

At threshold stimulus intensities there was no PSP detectable in 41% of the cases. The mean PSP amplitude during 5-HT application, averaged over all cells tested (\( n = 44 \)) and all stimulus intensities, was 46.2 ± 23.4% (41.9 ± 25.9%) of the corresponding control values. Similar reductions were found for maximal slope and time integral: 45.7 ± 23.7% (42.3 ± 26.4%) and 61.4 ± 28.4% (55.6 ± 28.1%), respectively. On the other hand, 5-HT had virtually no effect on the decaying phase of the PSPs (mean \( t_{1/2} \) of 97.1 ± 41.9% and 87.9 ± 41.3%). In the following, the analysis will therefore be limited to amplitude, maximal slope, and time integral. After removal of 5-HT from the medium, the PSPs recovered usually within 30–60 min (Fig. 6). Because, as shown in a previous paragraph, 5-HT depolarizes PN neurons, it has to be ruled out that the reduction of PSP amplitude is based on depolarization at the synaptic sites in dendrites with a consecutive reduction of driving force. This might be the case if the compensatory current did not reach the synaptic site due to a possible space-clamp error. Three arguments will be presented in detail in the following paragraphs that indicate that this is not the case. First, voltage-sensitive changes of the form of PSPs could be readily modulated under control and 5-HT conditions using somatic current injections. This fact demonstrated that current injected at the soma indeed reaches postsynaptic sites. Second, 5-HT effect on PSPs was observed under selective pharmacological blockade of the 5-HT–induced depolarization. Third, 5-HT showed frequency-dependent effects on paired-pulse facilitation, supporting the notion of a presynaptic 5-HT effect.

We have recently shown in detail that the amplitude of excitatory PSPs is independent of the SMP over a wide range of SMPs (Möck et al. 1997). To test whether this independence is preserved during 5-HT application, we recorded medium-sized PSPs (5–10 mV at resting SMP under control conditions) at various SMPs. The representative example shown in Fig. 7A clearly shows the typical results found in PN neurons under control conditions: the amplitude remained fairly constant across the entire range of SMPs tested. Note, however, that the PSP decay is strongly influenced by depolarizing current injection at the soma. As described elsewhere (Möck et al. 1997), this current injection removes the \( \text{Mg}^{2+} \) block from \( \text{N-methyl-D-aspartate (NMDA)} \) receptor-gated channels and possibly activates the persistent sodium conductance. Application of 5 \( \mu \)M 5-HT reduced the PSP amplitude as expected (Fig. 7B) but did not alter its independence from the SMP (Fig. 7C).

Does this reduction of PSPs mean that synaptic transmission on PN neurons is less effective in the presence of 5-HT, resulting in a decreased cerebrocerebellar information transfer? To answer this question, it has to be taken into account that 5-HT, while diminishing the PSP amplitude, also depolarized the SMP by several millivolts. Thus the crucial factor for pontine signal transmission under 5-HT is the effective peak depolarization reached at the somatic zone of spike generation under both conditions. We, therefore determined the “total” depolarization as the sum of PSP amplitude and the net steady-state depolarization under 5-HT (this calculation was done because the steady-state potential was compensated before recording PSPs) and compared it with the control PSP. The mean difference in peak depolarization was found to vary from case to case, but on average was negligible (–0.05 ± 5.5 mV, \( n = 38 \)). Since 5-HT did not alter the firing threshold in PN neurons, the conclusion would be that, on average, single PSPs are equally effective in driving PN neurons under both conditions. In line with this conclusion, we found in four cases in which our stimulus protocol was applied without compensating the 5-HT–induced depolarization of the SMP, spike generation under control and test conditions were at similar stimulus strengths.

In many neurons, synaptic transmission is not invariant during repetitive stimulation, but rather is influenced by previous events. The synaptic transmission on PN neurons is known to show robust paired-pulse facilitation (PPF) at interstimulus intervals between 10–200 ms (Möck et al. 1997). Two questions motivated us to study whether 5-HT also modulates PPF in the PN. First, alteration of PPF would indicate a presynaptic site of 5-HT action on synaptic transmission, whereas an unaltered PPF would argue for a postsynaptic site. Second, modulation of PPF in either direction would have strong functional implications, since, as shown above, the net effectiveness of a single PSP was unchanged by 5-HT. To this end, we applied pairs of electrical stimuli with delays between 10 and 1,000 ms at sites in the cerebral peduncle under control conditions and during 5-HT application. The amount of facilitation was determined by comparing the amplitude of the two PSPs evoked by the two stimuli. At the smallest interstimulus intervals (10 ms, or in some, 20 ms) the resulting PSPs overlapped in time. To obtain the isolated second PSP in these cases, we subtracted an average control PSP. Typical results for PPF in PN neurons are presented in Fig. 8. In this example, we observed weak PPF for long interstimulus intervals. Typically, PPF increased with shorter intervals between the pulse-pair length (Fig. 8, A and B) and was seen in all cases examined. In the example shown in Fig. 8B, the strongest enhancement of synaptic transmission occurred at a delay of 50 ms. Application of 5-HT expectedly reduced the amplitudes of both PSPs elicited by the paired stimuli (Fig. 8, C and D). As in the control recording, we observed a clear facilitation of the second PSP for shorter interstimulus intervals, whereas it was weak with longer delays. Quantification of the amount of facilitation (as percentage of the control amplitude) revealed that in the example shown, the PPF under 5-HT was about the same for longer interstimulus intervals as the one observed under control conditions (Fig. 8E). However, 5-HT enhanced the facilitation of the second PSP if the interval between pulses was short (10 and 20 ms). The summary plot in Fig. 8F demonstrates that 5-HT exerted similar effects on all cells tested (\( n = 6 \)). Finally, we statistically analyzed the differences in the amount of facilitation for each class of interstimulus intervals over the entire population. It turned out that 5-HT significantly enhanced PPF at the smallest intervals (10 and 20 ms; \( P < 0.05 \)), while the difference at larger intervals did not reach significance (\( P > 0.1 \)). What is the reason for this
differential, frequency-dependent modulation of PPF? Before attributing a presynaptic action to the observed 5-HT effect, a possible saturation of PSP amplitudes at shorter intervals under control conditions (e.g., due to glutamate receptor saturation) has to be ruled out. If the enhanced PPF under 5-HT for smaller intervals were due to a ceiling effect, it could be expected that the ratio between PPF under 5-HT and PPF under control conditions (PPF_{5-HT}/PPF_{control}) would increase monotonically with shorter interstimulus intervals. Investigating the mean PPF_{5-HT}/PPF_{control} across interstimulus intervals (Fig. 8G) revealed a sigmoidal relationship, which indicates that PPF is subject to saturation under both conditions. A second argument against a ceiling effect of PPF at the shortest interstimulus interval is provided by the observation in two cells that PPF under 5-HT is similar at different stimulus intensities (202 ± 13.6% vs. 201 ± 19.9% at 3 times higher stimulus intensity than that which evoked a similar PSP amplitude after a single pulse, observed for the lower intensity under control condi-
tions; the interstimulus intervals of 10 ms was investigated). Having thus ruled out a postsynaptic saturation of PSP amplitudes, a possible presynaptic explanation is based on the known fact that the releasable transmitter pool is partly depleted at central synapses for a few 10s of milliseconds after transmitter release, i.e., the release sites are refractory for a short period in which the amplitude of a second PSP is negatively correlated to the amplitude of a preceding one (for references and discussion see Thomson 2000). Such a mechanism might convincingly explain two of the most salient results from our PPF experiments: 1) under control conditions the amount of PPF drops at very short interstimulus intervals possibly because the immediately releasable transmitter pool is still not fully recovered at the time the second pulse enters the terminals and 2) due to the inverse correlation of the amplitudes of consecutive PSPs during refractoriness, the 5-HT–

FIG. 6. 5-HT effects on synaptically evoked postsynaptic potentials. A: electrical stimulation (120 μA, 0.1-ms duration) of afferent fibers within the cerebral peduncle evoked postsynaptic potentials (PSPs) in pontine neurons, which increased in amplitude with increased stimulus intensities. The presented PSPs are, as in other figures, averages of 10 individual PSPs subsequently recorded at each stimulus intensity. All recordings the membrane potential was, if necessary, readjusted to the control value. During application of 5 μM 5-HT, the magnitude of these PSPs was substantially reduced at any stimulus intensity. After removing 5-HT from the bath, the PSPs recovered within 30 min. In this example, 30-μA stimulation was strong enough to elicit a spike. Application of 5-HT plus cyanopindolol after the recovery from 5-HT did not result in a similar reduction of the PSPs. Their magnitude was similar to the corresponding control and recovery recordings. B: average PSPs recorded in a different PN neuron but following a similar protocol as in A (except for maximal stimulus intensity). As in A, 5-HT strongly and reversibly reduced the magnitude of the PSPs at any stimulus intensity. A similar reduction in magnitude was observed during coapplication of 5-HT and cinanserin. C: quantified data showing amplitude, maximal slope, and time integral of the PSPs in A and B (conventions as in Fig. 6). 5-HT (white squares) reduced amplitude and maximal slope to about 30% of the control value (black circles) at any given SMP. The integral was reduced to a lesser extent at more negative SMPs. Its stronger reduction at less negative potentials is explained by the lack of activation of voltage-dependent boosting mechanisms due to the small PSP amplitude.

FIG. 7. 5-HT effects voltage dependence of postsynaptic potentials. A: average PSP (n = 10) recorded in a PN neuron at different SMPs under control conditions. They were evoked by electrical stimulation (120 μA, 0.1-ms duration) within the cerebral peduncle. PSP amplitude was almost independent of SMP. B: same neuron, stimulation, and recording protocol as in A, tested for the voltage dependence of the PSP during 5-HT application. Expectedly, the magnitude of the PSP was largely reduced by 5-HT, but it displayed an unchanged voltage dependence. C: quantified data showing amplitude, maximal slope, and time integral of the PSPs in A and B (conventions as in Fig. 6). 5-HT (white squares) reduced amplitude and maximal slope to about 30% of the control value (black circles) at any given SMP. The integral was reduced to a lesser extent at more negative SMPs. Its stronger reduction at less negative potentials is explained by the lack of activation of voltage-dependent boosting mechanisms due to the small PSP amplitude.
FIG. 8. Serotonergic modulation of paired-pulse facilitation (PPF). A: averaged postsynaptic response (n = 10) recorded in a PN neuron after paired stimulation within the cerebral peduncle (20 μA, 0.1-ms duration each, 20-ms interstimulus interval) under control conditions. The conditioning pulse strongly facilitated the response to the 2nd one. B: averaged (n = 10) control and isolated 2nd PSPs (top) and difference between control and isolated 2nd PSP (bottom) for all interstimulus intervals used. Recordings were from the same neuron in A. Isolated 2nd PSPs were obtained by subtracting the control PSP from the responses to paired stimuli. A substantial facilitation was observed for shorter interstimulus intervals. C: averaged postsynaptic response (n = 10) recorded during 5-HT application in the same neuron and using the same protocol as in A. The 5-HT–induced depolarization was compensated by current injection. As expected, the amplitude of the individual PSPs was reduced as compared with the control, but the pairing paradigm still elicited a strong facilitation of the second PSP. D: same neuron and conventions as in B during 5-HT application. Compared with the control, the facilitation of the second pulse was pronounced for short intervals. E and F: quantification of paired-pulse facilitation for the example shown in A–D (E) and for the entire sample (F). The amount of facilitation is expressed as percentage of the amplitude of the control PSP. As compared with control conditions, the maximum facilitation is increased and shifted to higher frequencies. The shift of facilitation to higher frequencies is reflected in the population data (F). The box-and-whisker plot shows medians by horizontal bars, 25–75% quartiles by boxes, and the range by vertical bars. Statistical analysis revealed no significant difference between both conditions for interstimulus intervals between 1,000 and 50 ms, but, as indicated by an asterisk, the amount of paired-pulse facilitation is significantly enhanced by 5-HT for interstimulus intervals of 20 and 10 ms. G: ratio between PPF during 5-HT application and during control conditions. Mean ratios ± SE are plotted vs. interstimulus intervals. The ratios are close to 1 for long interstimulus intervals (>100 ms) but increase for interstimulus intervals between 100–10 ms. Note however, that this increase is not monotonic. For those interstimulus intervals resulting in a significant increase in PPF during 5-HT application (20 and 10 ms; see G), the ratios are almost similar.
induced reduction of the first PSP, reflecting a minor depletion of the releasable transmitter pool, may result in a stronger facilitation at very short interstimulus intervals as compared with control conditions. In summary, at short interstimulus intervals, facilitation is partly counterbalanced by a depletion-based depression. 5-HT might reduce depletion and therefore emphasize facilitation.

**Pharmacology of 5-HT–induced modulation of PSPs**

Modulation of PPF indicates a presynaptic 5-HT action within the PN. Presynaptic action of 5-HT has been shown to be mediated by 5-HT$_1$ receptors in other brain structures (Hwang and Dun 1999; Li and Bayliss 1998; Muramatsu et al. 1998; Schmitz et al. 1995a,b, 1998a,b; Wang et al. 1999). However, there is also evidence that 5-HT$_2$ receptors are located on nerve terminals (Jakab and Goldmann-Rakic 1998). To decide between these two possibilities, we coapplied 5-HT with cinanserin or cyanopindolol while electrically stimulating at sites within the cerebral peduncle. Representative examples of these experiments and their quantitative analysis are given in Fig. 6. As has been described before, 5-HT strongly but reversibly reduced the amplitude, maximal slope, and time integral in both cases. During blockade of 5-HT$_1$ receptors with 10 μM cyanopindolol, 5-HT did not exert similar effects on the PSP (Fig. 6A and C). All of the PSP parameters, modulated by 5-HT application before, now paralleled the values determined from recordings after recovery from 5-HT action (Fig. 6C). As cyanopindolol is specific for 5-HT$_1$ receptors, the SMP depolarization, which is based on 5-HT$_2$ action, was present in these experiments and was compensated for by current injection into the soma. The successful blockade of 5-HT-induced decrement of PSPs under these conditions proves that this effect is due to genuine 5-HT action on synaptic transmission and cannot be explained by a reduced driving force due to lack of space-clamp control at the postsynaptic (dendritic) site. In contrast, blocking 5-HT$_2$ receptors with 20 μM cinanserin was ineffective in preventing serotonergic modulation of PSPs (Fig. 6B and D). The PSPs were clearly reduced in magnitude compared with the control and recovery recordings, but similar to those during 5-HT application alone at any given stimulus current amplitude. Accordingly, the quantified values for amplitude, maximal slope, and time integral closely paralleled those obtained during 5-HT application (Fig. 6D). The observation of diminished PSPs in the presence of cinanserin provides further evidence against a role of depolarization in the 5-HT–induced reduction of PSPs. We conclude that 5-HT reduces synaptic transmission on PN neurons by acting on 5-HT$_1$ receptors.

**Discussion**

In this study, we demonstrate that information processing and information transfer in the PN is strongly modulated by 5-HT. First, activation of 5-HT$_2$ receptors increases the excitability of these neurons mainly based on depolarization of the somatic membrane potential, increases the apparent input resistance, increases inward rectification in depolarizing direction, and decreases the mAHP amplitude. Second, mediated by 5-HT$_1$ receptors, 5-HT decreases postsynaptic potentials in PN neurons. Third, the short-term facilitation of synaptic inputs on PN neurons is selectively enhanced for high-frequency inputs. In the following we will discuss the possible mechanisms of 5-HT action and argue that the PN may function as a high-pass filter gate during periods of serotonergic modulation.

**Location and mechanisms of 5-HT action**

5-HT has attracted a lot of interest since it has been assumed to play a crucial role in the regulation of behavioral states. Accordingly, a considerable amount of work has been done in many brain regions to unravel the molecular and ionic mechanisms underlying 5-HT action. The diversity of receptor subtypes, second messenger systems, and ionic conductances presently known to be involved is enormous, and yet, the net effects on individual neurons described so far may be assigned to only a few pharmacological categories. On the one hand, 5-HT either increases or decreases the excitability. On the other hand, it reduces or enhances synaptic transmission. Finally, it can change the firing pattern.

Increased excitability has been described in neocortical (Araneda and Andrade 1991; Davies et al. 1987; McCormick and Williamson 1989; Sheldon and Aghajanian 1990) and hippocampal (Andrade and Chaput 1991; Andrade and Nicoll 1987; Bijak and Misgeld 1997; Colino and Halliwell 1987; Gasparini and DiFrancesco 1999; Siarey et al. 1995) pyramidal and interneurons, thalamic neurons (McCormick and Pape 1990; McCormick and Wang 1991; Pape and McCormick 1989), inferior olive neurons (Placantonakis et al. 2000), and cranial neurons (Hisao et al. 1997, 1998; Larkman et al. 1989), as well as spinal motoneurons (Berger and Takahashi 1990; Kjaerulff and Kiehn 2001). Commonly this increase is, as in our case, accompanied by depolarization. In the aforementioned studies, several mechanisms have been discussed to underlie depolarization: reduction of potassium conductances like the leak K$^+$ conductance, inward rectifying K$^+$ conductances, and $I_{\text{M}}$ or enhancement of $I_{\text{H}}$ and $I_{\text{F}}$. In PN neurons, there is no convincing evidence for the presence of $I_{\text{M}}$ and $I_{\text{F}}$, and only a small portion of cells may possess $I_{\text{H}}$ (Schwarz et al. 1997). Therefore these conductances most probably do not contribute substantially to the depolarization described here. A depolarization based on the reduction of K$^+$ conductances would also be in accordance with the observed increase in $R_{\text{in}}$. Although we cannot rule out a modulation of $I_{\text{leak}}$, the most likely candidates in PN neurons are the fast inwardly rectifying $I_{\text{Kir}}$ and probably an unidentified outward rectifying K$^+$ conductance. Both were previously described in PN neurons.

**Table 2. Quantified data for pharmacology of 5-HT effects on postsynaptic potentials**

<table>
<thead>
<tr>
<th>5-HT/Cyanopindolol (n = 6)</th>
<th>5-HT/Cinanserin (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of control amplitude</td>
<td>84.8 ± 15.7 (88.5 ± 21.2*)</td>
</tr>
<tr>
<td>Percentage of control maximal slope</td>
<td>87.3 ± 9.6 (71.9 ± 21.7*)</td>
</tr>
<tr>
<td>Percentage of control time integral</td>
<td>88.0 ± 13.1 (74.7 ± 23.5*)</td>
</tr>
<tr>
<td>Percentage of control time integral</td>
<td>31.8 ± 14.3 (47.0 ± 33.7*)</td>
</tr>
<tr>
<td>Percentage of control time integral</td>
<td>39.5 ± 21.2 (36.9 ± 22.1*)</td>
</tr>
<tr>
<td>Percentage of control time integral</td>
<td>39.6 ± 19.6 (33.8 ± 17.2*)</td>
</tr>
</tbody>
</table>

Values are ± SE. See Table 1 for definitions.

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Ca<sup>2+</sup> Inoue and et al. (1999) showed that serotonergic action on a long-lasting increase in excitability. Most studies on serotonergic modulation of AHPs report a reduction of the long-lasting sAHP due to a reduction of the Ca<sup>2+</sup>-dependent K<sup>+</sup> current I<sub>AHP</sub> (Andrade and Chaput 1991; Andrade and Nicoll 1987; Colino and Halliwell 1987; McCormick and Williamson 1989). However, Inoue et al. (1999) showed that serotonergic action on a Ca<sup>2+</sup>-dependent K<sup>+</sup> current could also reduce the amplitude of mAHPs. The mAHPs in PN neurons were shown to be composed of a Ca<sup>2+</sup>-dependent and a Ca<sup>2+</sup>-independent component (Schwarz et al. 1997). Therefore the mechanism described by Inoue et al. (1999) might account for the mAHP reduction in PN neurons.

Functional considerations

In this paper, we described opposing effects of 5-HT in the PN, namely an increase in excitability of the membrane and a reduction in excitatory synaptic transmission. As detailed in RESULTS, the amount of 5-HT-induced depolarization and single PSP amplitude reduction almost perfectly balance each other out at stimulus intensities high enough to drive the cell close to the firing threshold. On this basis it could be assumed that the net effect of serotonergic modulation in the PN is to increase the firing rate by reducing mAHPs and increasing R<sub>in</sub>. An additional function of serotonergic modulation is, however, suggested by its effect on synaptic facilitation. Under control conditions in vitro, there is already a robust frequency-dependent facilitation for synaptic inputs arriving at intervals <200 ms. In this situation, the strongest facilitation was observed for intervals of 50 and 20 ms, and it dropped substantially for shorter ones (Möck et al. 1997). Thus synapses impinging on PN neurons possess a mechanism to gate inputs to these cells according to their temporal structure even under control conditions in vitro. Our finding of selective enhancement of synaptic facilitation for high-frequency input by 5-HT indicates a strengthening of the high-pass filter characteristics of the synaptic transmission onto PN neurons. Therefore during periods of 5-HT release, the effectiveness of high-frequency inputs to drive PN neurons may be increased compared with low-frequency inputs. Interestingly, a similar modulation of gating properties by acetylcholine and noradrenalin was recently described for corticothalamic synapses (Castro-Alamancos and Calcagnotto 2001).

To understand the functional significance of serotonergic modulation of PN neurons, one must consider the activity pattern within the sources of their serotonergic afferents. The PN receive serotonergic input from pontine as well as from medullary raphe nuclei (Mihailoff et al. 1989). The neurons in both groups are most active during periods of alertness and active behavior (Veasey et al. 1995, 1997). They differ, however, in their responses during active motor performance. Nearly all neurons located within the medullary raphe nuclei, which also provide input to the inferior olive (Bishop and Ho 1986; Compoint and Buisseret-Delmas 1988), display their maximal firing rates during motor activities (Veasey et al. 1995).
SEROTONERGIC MODULATION IN PONTINE NUCLEI

Hamada S, Senzaki K, Hamaguchi-Hamada K, Tabuchi K, Yamamoto H, Yamamoto T, Yoshikawa S, Okano H, and Okado N. Localization of 5-HT_1A receptor in rat cerebral cortex and olfactory system revealed by immunohistochemistry using two antibodies raised in rabbit and chicken. 


Hsiao CF, Del Negro CA, Trueblood PR, and Chandler SH. Iomic basis for serotonin-induced bistable membrane potential properties in guinea pig trigeminal motoneurons. 


Hsiao CF, Trueblood PR, Levine MS, and Chandler SH. Multiple effects of serotonin on membrane properties of trigeminal motoneurons in vitro. 


Hwang LL and Dun NJ. Serotonin modulates synaptic transmission in immature rat ventrolateral medulla neurons in vitro. 


Jacobs BL and Azmitia EC. Structure and function of the brain serotonin system. 


Jakab RL and Goldman-Rakic PS. 5-Hydroxytryptamine 1A serotonin receptors in the primate cerebral cortex: possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. 


Kjaerulff O and Kehin O. 5-HT modulation of multiple inward rectifiers in motoneurons in intact preparations of the neonatal rat spinal cord. 


Leggio CR, Mercier B, and Gluckstein M. Corticopontine projection in the rat: the distribution of labelled cortical cells after large injections of horseradish peroxidase in the pontine nuclei. 


Li Y-W and Barylss DA. Presynaptic inhibition by 5-HT_1B receptors of glutamatergic synaptic inputs onto serotonergic caudal raphe neurons in rat. 


Lopez-Garcia JA. Serotonergic modulation of the responses to excitatory amino acids of rat dorsal horn neurons in vitro: implications for somatosenosory transmission. 


Mc Cormick DA and Pape H-C. Noradrenergic and serotonergic modulation of a hyperpolarization-activated cation current in thalamic relay neurons. 


Mc Cormick DA and Wang Z. Serotonin and noradrenaline excite GABAergic neurons of the guinea-pig and cat nucleus reticularis thalami. 


Mc Cormick DA and Williamson A. Convergence and divergence of neurotransmitter action in human cerebral cortex. 


Mihaloff GA, Kosinski RJ, Azizi SA, and Border BG. Survey of noncor tical afferent projections to the basilar pontine nuclei: a retrograde tracing study in the rat. 


Moll M, Schwarz C, and Theiner P. Electrophysiological properties of rat pontine nuclei neurons in vitro. II. Postsynaptic potentials. 


Muramatsu M, Lapi NDS, Tanaka E, and Grendhoff J. Serotonin inhibits synaptic glutamate currents in rat nucleus accumbens neurons via presynaptic 5-HT_1B receptors. 


Murase K, Randic M, Shirasaki T, Nakagawa T, and Akaie N. Serotonin suppresses N-methyl-D-aspartate responses in acutely isolated spinal dorsal horn neurons of the rat. 


Okumura DY and Beck SG. 5-HT_1A receptor linked to inward-rectifying potassium current in hippocampal CA3 pyramidal cells. 


REFERENCES

Andrade R and Chaput Y. 5-Hydroxytryptamine-like receptors mediate the slow excitatory response to serotonin in the rat hippocampus. 


Andrade R and Nicolai RA. Pharmacologically distinct actions of serotonin on single pyramidal neurons of the rat hippocampus recorded in vitro. 


Anwyl R. Neurophysiological actions of 5-hydroxytryptamine in the verte brate nervous system. 


Araneda R and Andrade R. 5-hydroxytryptamine, and 5-hydroxytryptamine_1A receptors mediate opposing responses on membrane excitability in rat association cortex. 


Bergen AJ and Takahashi T. Serotonin enhances a low-voltage-activated calcium current in spinal motoneurons. 


Biak M and Msegel U. Effects of serotonin through serotonin_1A and serotonin_1D receptors on inhibition in the guinea-pig dentate gyrus in vitro. 


Bishop GA and Ho RH. Cell bodies of origin of serotonin-immunoreactive afferents to the inferior olivary complex of the rat. 


Castro-Alamancos MA and Calcagnotto ME. High-pass filtering of corticothalamic activity by neuromodulators released in the thalamus during arousal: in vitro and in vivo. 


Colino A and Halliwell JV. Differential modulation of three separate K-conductances in hippocampal CA1 neurons by serotonin. 


Compartment C and Buisseret-Delmas C. Origin, distribution and organization of the serotonergic innervation in the inferior olivary complex of the rat. 


Corne-Herbert V, Riad M, Wu C, Singh SK, and Descarries L. Cellular and subcellular distribution of the serotonin 5-HT_1A receptor in the central nervous system of adult rat. 


Davies MF, Deen Y, Prince DA, and Peroutka SJ. Two distinct effects of 5-hydroxytryptamine on single cortical neurons. 


DeFilipe J, Arelano JI, Gómez A, Azmitia EC, and Munoz A. Pyramidal cell axons show a local specialization for GABA and 5-HT inputs in monkey and human cerebral cortex. 


Fornal CA, Metzler CW, Markos F, Rivero-Do-Valle LE, and Jacobs BL. A subgroup of dorsal raphe serotonergic neurons in the cat is strongly activated during oral-buccal movements. 


Gasparini S and Di Francesco D. Action of serotonin on the hyperpolarization-activated cation current (I_h) in rat CA1 hippocampal neurons. 


Goldstein M, Battista AF, Nakatani S, and Angagostile B. The effects of centrally acting drugs on tremor in monkeys with mesencephalic lesions. 


